REMARKS

Applicants thank the Office for the attention accorded the present Application in the July 28, 2004, Office Action. In that Action, Claims 1-10 and 17-18 were rejected under 35 USC §103(a) as being unpatentable over Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. in view of Rork et al., and Claim 18 was allowed.

The Office admits that the references Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. do not expressly teach the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, and HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single dosage unit.

The Office cites Rork et al. for the proposition that Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol with HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single once-a-day dosage unit.

The Office relies on Rork et al. and the knowledge of one of ordinary skill in the art to establish a prima facie case of obviousness, and then responds to Applicants' previous arguments by stating that the arguments are not found persuasive.

The Office's reliance on *In re Kerkhoven* is incorrect because the Office takes *In re Kerkhoven's* s narrow findings regarding two chemical compositions that each promotes the formation of a nodular structure In cast iron and then generalizes the narrow finding to a broader one. The "very same purpose" in *In re Kerkhoven* is promoting the formation of a nodular structure. The Office discounts the fact that the purpose (mechanism of action) of each component in Applicants' claimed invention is different and states that Applicants' combination is for the same "thing" (not purpose), i.e. reducing the risk of cardiovascular disease.

The Office further states that the Applicants apparently confuse "mechanism of action" with "therapeutic goal." The Office goes on to state that statins and betablockers, as taught in the prior art, are useful for reducing the risk of cardiovascular disease individually. To support its obviousness conclusion and its reliance on *In re Kerkhoven* in support of its conclusion, the Office provides many examples from the pharmaceutical art. The Office states

> "As a matter of fact, in the pharmaceutical art, there are so many examples that two drugs having different mechanism of action but for the same purpose as concomitantly employed together; to name a few: asthma treatment: corticosteroids and beta-2 agonists together; allergy medicine: combining antihistamine and nasal decongestant; antihypertension medicine: calcium channel blocker plus ACE inhibitor together, angiotensin-2 inhibitor and diuretic together; anti-diabetic: metformin plus troglitazone and/or insulin; anti-cancer: almost always using multi-drug treatment; anti-infective: Sulfamethoxazole and trimethoprim (Bactrim DS); GI: antacid plus H2-inhibitors; and erectile dysfunction treatment: Papaverine, Phentolamine, and PGE1 together (Trimix). The examples listed above are drugs that are having a very different mechanism of action and yet being combined for the very same therapeutic goal." (Office Action Page 6, last paragraph to Page 7).

The Office's reliance on *In re Kerkhoven*, its reasoning and arguments still fall short of sustaining its prima facie case of obviousness. The Office attempts to use examples of combined medications to support its conclusion that *In re Kerkhoven* is being appropriately applied; that two medications used separately for the same therapeutic goal would render their combination into a single dosage unit obvious because they are used for the same purpose. The Office is trying to use circular reasoning to justify its obviousness conclusion by pointing to a number of examples that also have the very same therapeutic goal. Applicants submit that the Office's broadening of the holding in *In re Kerkhoven* is incorrect.

Applicants offer into evidence the following issued U.S. patents of composition of medications, some of which are compositions cited by the Office. Under the Office's interpretation of *In re Kerkhoven*, the medications in these valid, issued, U.S. patents would be considered to be "combined for the same therapeutic goal." Yet, they are considered novel and nonobvious by there being allowed as valid U.S. patents in spite of the holding in *In re Kerkhoven*.

For example, U.S. Patent No. 6,455,524 (Bozung et al.) claims a composition that combines anticholinergic and beta-sympathomimetic drugs. The therapeutic entities differ in the mechanism of action by which they produce a beneficial effect. One blocks cholinergic pathways and the other stimulates adrenergic receptors. Each is know to be individually useful in treating human beings for "respiratory ailments." Applicants take notice that, while each is used for the purpose of treating "respiratory

ailments," the patent is predicated upon each drug accomplishing a similar broad goal by a different mechanism of action from each other.

U.S. Patent No. 3,985,876 (Hazlett et al.) claims compositions that combine sulfamethoxazole and trimethoprim (Bactrim, as noted by the Office) in a solution. The drug entities differ in mechanisms of action by which they produce a beneficial effect. One competes with synthetic pathways by blocking para-aminobenzoic acid and the other inhibits the enzyme dihydrofolate reductase. Each drug is known to be useful to provide an "anti-infective" benefit for human beings with infections, yet each provides an "anti-infective effect" through a different mechanism of action.

U.S. Patent 4,125,610 (Redl, George) claims compositions that combine phosphanilic acid and trimethoprim.

U.S. Patent No. 5,10,675 (Cho et al.) claims compositions that combine antihistamine, analgesic and decongestant. The drug entities, all known to be used for respiratory disorders such as rhinitis and sinusitis, differ in the mechanism of action by which they produce a beneficial effect. One blocks mast cell histamine receptors, one acts upon prostaglandin pathways, and one stimulates adrenergic receptors. Applicants point out that each drug accomplishes a different therapeutic goal in treating respiratory disorders.

U.S. Patent No. 6,214,837 (Bloomqvist, Goran) claims combinations that combine two medications that have different therapeutic actions, quinine and antihistamine, to treat the affliction called "restless legs." "Restless legs" is a tingling

and feeling of crawling in the lower legs that occurs particularly at night and affects especially older patients.

U.S. Patent No. 5,632,975 (Earles, R. Martin) claims compositions that combine hydrocortisone, elemental sulfur, a neutral hydrocarbon jelly, and carboxypolymethylene. The therapeutic entities differ in the mechanism of action by which they produce a beneficial effect as a "dermatitis treatment." Each accomplish a different therapeutic goal.

U.S. Patent No. 4,217,347 (Horovitz, et al.) claims formulations of angiotensin converting enzyme inhibitors and diuretics. Both agents are known to be useful to treat hypertension, however, they provide therapeutic benefit by different modes of action.

This evidence supports Applicants' contention that the Office's current interpretation under *In re Kerkhoven* (that the two drugs, statins and beta blockers, of the present invention accomplish the same therapeutic goal, i.e. reducing cardiovascular risk) is inappropriate and is incompatible with the Office's own history on allowability of these types of inventions.

The Office maintains its reliance on Rork et al. to teach the use of beta-blockers **and** lipid-lowering agents. Applicants disagree and submit Applicants' prior arguments as evidence that Rork et al. teach the use of beta-blockers **or** lipid-lowering agents **or** any **one** of the active agents in the long list provided in the Rork disclosure. Rork contains no teaching, suggestion, motivation, or scientific data to use the device for other than a single drug agent. It is the Office's use of hindsight that provides the link to

support the obviousness rejection. Applicants have provided evidence in the form of numerous publications and two Declarations that support a finding of nonobviousness. Despite Applicants' evidence, the Office relies on its own conclusion (not further evidence of a teaching or suggestion or motivation in the cited prior art to counter Applicants' evidence) to maintain its obviousness rejection. The only evidence the Office provides is a statement of examples in the pharmaceutical art to support its contention that two drugs having different mechanism of action but for the same purpose are concomitantly employed together. Yet, these very same examples are all protected by patent for being novel and nonobvious.

Conclusion

It is clear that, when Applicants' invention is viewed as a whole, the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. On the other hand, Applicants have provided evidence of noncompliance problems, the under-utilization of medications and the Declarations of Dr. Gurwitz and Dr. Dean (previously submitted) as to the healthcare industries' struggles to find answers to these perplexing questions.

In light of the above arguments, Applicants respectfully submit that Claims 1-10

and 17-18 of the present application contain allowable subject matter and that the 35 USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

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Robert R. Deleault, Reg. No. 39,165
Attorney for Applicants
41 Brook Street
Manchester, NH 03104
Tel. (603) 668-1971
Fax (603) 622-1445

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